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Online Intervention for Prevention of Major Depression

To the Editor The article by Ms Buntrock and colleagues[1] presented data on primary prevention of major depression in patients who did not exhibit prior depressive episodes or secondary prevention in patients who had prior depressive episodes using an online intervention. Only 6 one-hour sessions provided a substantial and sustained effect for 1 year. If a major depressive episode is already present, usually 12 to 20 individual sessions of cognitive behavioral therapy are needed to achieve response or remission,[2] although fewer may also be effective.[3] However, some issues should be clarified.

First, could the authors explain the abrupt decrease in number of participants without a major depressive episode found in both treatment groups, but especially in the control group, after 26 weeks (Figure 2 in the article)?

Second, an online trainer was used in the intervention group. Although the trainer did not perform psychotherapy, it would be important to know if the trainer intervened if more severe depressive symptoms, such as suicidal thoughts, were mentioned by the participants. Could this have influenced the outcome of the trial? How many hours were online trainers engaged in the guidance of patients?

Third, inpatient treatment rates and sickness leaves attributable to depression have substantially increased over the past decade[4,5] in Germany. Therefore, an intervention like the one described in the study could not only provide benefit for people with incipient symptoms and their health insurance arrangements, but also for psychiatrists, because they could focus on more severely ill patients who have already developed the full clinical syndrome but remain on long waiting lists for care. Furthermore, web-based treatment provides an opportunity for patients living in more remote areas to receive intervention.

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Conflict of Interest Disclosures: The author has completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

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In Reply We agree with Dr Anghelescu that it is remarkable that a major depressive episode can be prevented in people with subthreshold depression with a brief 6-session intervention. However, although this study was the first one showing that it is possible to prevent a major depressive episode using a web-based guided self-help intervention, evidence is accumulating that this can be achieved with brief face-to-face interventions.[1]

Providing low-threshold interventions for the treatment of subthreshold depression and the prevention of major depressive disorder may thus not only reduce substantial disease burden for the individual but also reduce societal costs. However, most clinical guidelines do not recommend psychological treatments for subthreshold depression. Given that effect sizes can be expected to be smaller than for the treatment of major depressive disorder, cost-effectiveness studies are needed to determine whether such an approach is good value for the money.

Anghelescu points out that there was a decrease in the number of participants without a major depressive episode in the survival analyses at 26 weeks. Participants who could not be reached at the last assessment point by diagnostic assessors after several attempts were censored at week 26 (midpoint assessment). Thus, we do not know whether the decrease reflects a loss in efficacy, because we do not know whether participants who were not reached experienced a major depressive episode or stayed healthy.

Another question referred to intensity and type of guidance provided by the online trainer, such as whether they intervened when suicidal thoughts were mentioned, and whether this might have influenced the results. The purpose of the guidance was not to deliver individual psychotherapy but to support participants in adhering to the treatment modules, which is typical for guided self-help interventions.[2] The total time a trainer spent per participant was 2 to 3 hours.[3] The online trainer provided semistandardized feedback on each of the completed modules using a standardized, preformulated text that was individually adapted based on what the participant wrote in the exercises.[4] Moreover, the online trainer regularly checked whether participants completed the intervention sessions on time and, if not, reminded them to do so. Trainers were advised not to deliver individualized psychotherapeutic strategies (such as techniques on how to handle suicidal thoughts), and this was assessed through fidelity checks by a supervisor. Hence, although we assume that the use of online trainers increased adherence and therefore the effectiveness of the intervention,[5] it is unlikely that effects were mediated by individually delivered psychological techniques.

Anghelescu also points out other potential benefits of web-based preventive approaches. Based on the results of this study and other emerging empirical evidence on preventive interventions for depression, implementing and disseminating such

low-threshold interventions on a large scale may eventually contribute to a reduction in the prevalence and burden of major depressive disorder.

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Conflict of Interest Disclosures: The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Ebert reported holding shares of the Institute for Online Health Training, which licenses the intervention studied from Leuphana University. No other disclosures were reported.

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Association of Infection in Early Life and Risk of Developing Type 1 Diabetes

To the Editor A research letter by Dr Beyerlein and colleagues focused on infections in early life and the risk of developing type 1 diabetes (T1D) in a large pediatric cohort.[1] We would like to address some relevant points about this study.

The authors did not assess some early determinants, such as gestational age, feeding practice (ie, breastfeeding), and perinatal use of antibiotics. These factors influence both gut development and function,[2] the risk of infections, and the consequent risk of T1D.

Also, choosing juvenile idiopathic arthritis (JIA) as a control autoimmune disease is questionable. Some proportion of children diagnosed with JIA in fact have a nonautoimmune systemic form, Still disease.[3]

Celiac disease, rather than JIA, would have been a better control condition because celiac disease shares with T1D a strong genetic background (ie, *HLA-DQ2*), as well as a common association with increased intestinal permeability.[4]

The gut microbiome is important in developmental programming and balanced helper T cell subtype 1 and subtype 2 (T_H1 and T_H2) immune homeostasis,[5] which is disrupted during autoimmune conditions such as T1D. Modulating the bacterial interface is crucial during the first 6 months of life. Thus potential influences on the microbiota should be considered in evaluating the risk to develop T1D.

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To the Editor The study by Dr Beyerlein and colleagues[1] is subject to an important confounder that challenges the validity of the association between infections and T1D. The prior administration of antibiotics has been strongly linked with the development of T1D both in empirical animal studies and in epidemiological studies.[2,3] The gut microbiota is thought to be critical to the development of the immune system. Eradication or depletion of the gut fauna adversely affects this process, increasing the risk of autoimmunity possibly by inducing anergy in pathways involved in self-tolerance.[2,3] Empirical animal models suggest that antibiotics in childhood, rather than infections, increase the risk of T1D.[2,3] The antibiotic model also would explain the precipitous rise in incidence of T1D over the past decades, at a mean annual rate of 3% as reported by the World Health Organization.[4] The misuse of antibiotics is an increasing global problem, with antibiotics administered inappropriately in viral infections.[5]A dose-response correlation is observed, whereby the greater the number of courses of antibiotics the greater the risk of T1D. Empirical and epidemiological studies both point to antimicrobials against gram-positive organisms as those most strongly associated with T1D.[2] A definitive interpretation of the study by Beyerlein and colleagues is difficult without adjusting for this confounder.

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